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Original citation & hyperlink:
Rahmani, Jamal et al. "Healthy Eating Index-2015 as a Predictor of Ulcerative Colitis Risk in a Case–Control Cohort". Journal of Digestive Diseases. 2019, 20(12). 649-655. https://dx.doi.org/10.1111/1751-2980.12826

DOI 10.1111/1751-2980.12826
ISSN 1751-2972
ESSN 1751-2980

Publisher: Wiley

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Healthy Eating and Ulcerative Colitis

ABSTRACT

Background & Aims: There is substantial compelling clinical evidence implicating certain dietary components in the development and clinical course of progression in ulcerative colitis (UC). The current study aimed to assess whether there exists any association between ulcerative colitis and scores on a healthy eating index.

Methods: In this case-control study, patients with UC were recruited and assessed along with healthy controls. Participants completed a validated 168 items food frequency questionnaire, the results of which were subsequently used to generate individual healthy eating index (HEI-2015) scores.

Results: Fifty-eight UC patients and 123 healthy controls were recruited. After controlling for confounding factors, subjects who were in the highest quartile of the HEI-2015 had a 66% lower odds ratio of UC when compared with the lowest quartile (OR = 0.34, 95% CI:0.12–0.96).

Conclusion: HEI-2015 was associated with UC in this cohort. Further elucidation of the role of key dietary elements is now warranted and required.

Keywords: healthy eating index-2015, ulcerative colitis, Diet, inflammatory bowel disease

INTRODUCTION

Chronic inflammation, which may be defined as persistent low-grade inflammation propagated by pro-inflammatory cytokines in tissues and circulation, putatively plays an important role in the pathogenesis and clinical course of inflammatory bowel disease (IBD) [1-3]. In line with this, chronic inflammation is known to be an important factor in mediating the development of ulcerative colitis (UC) [4], which is characterized by bloody diarrhea, abdominal pain and weight loss, as well as several extra-intestinal manifestations [5]. UC also features a remitting-relapsing course, with consequent morbidity [6].

UC is attributed to the multifaceted interactions of various environmental, hereditary, and immunoregulatory factors [7]. Diet influences gastrointestinal inflammation through numerous mechanisms, including direct antigen presentation, altered prostaglandin regulation, and changes in the composition or functionality of the intestinal microbiome [8,9]. There have been a number of attempts to tease apart the associations between dietary intake and UC, with several food groups being highlighted previously as contributory or protective [10-12]. In a comprehensive systematic review, Hou and colleagues [12] uncovered an increased risk of UC development in individuals who report high total fat, PUFA (specifically omega-6 fatty acids), and meat intake. In contrast, there have not been any consistent associations uncovered between total daily carbohydrate intake and risk of IBD development.

It is evident that diet represents a variable and complex array of environmental exposures which modulate inflammatory response and, ultimately, impact substantially upon overarching health outcomes. With this in mind, numerous diet quality questionnaires have been developed and validated to provide standardized measurements of overall diet quality for the study of such interactions. These include the Diet Quality Index [13,14], the Diet Diversity Score [15], and the Healthy Eating Index [16,17]. There is also a dietary inflammatory index, which is intended to predict the inflammatory potential of the diet through validated associations with certain markers of inflammation, including C-reactive protein [18,19], interleukin-6 [18,20], and homocysteine [18]. Dietary indices been shown to be relevant in the settings of glucose intolerance [19], shift work status [19], asthma [20], obesity [21] and various cancers (colorectal, pancreatic and prostate) [18,22,23].

The Healthy Eating Index-2015 (HEI-2015) has been used widely in the assessment of dietary quality. This tool has been applied to a range of clinical research study designs to identify and assess associations among cumulative diet quality and specific disease outcomes, such as risk of mortality by cardiovascular disease [24]. In addition, the index has also been utilized in several

population subgroups [25], children [26,27], cancer survivors [28], and in investigating the effects of race [29]. The HEI provides a total score, which is energy adjusted and provides information on the general quality of the individual's dietary behaviour. Finally, the tool generates 13 individual component scores that are examined concurrently in order to identify any complex dietary patterns or interactions, thereby providing more detail and power to detect associations than other dietary questionnaires.

To date the HEI has not been evaluated in the context of UC. Given the complex etiology of UC and the known effects of dietary factors, the present study aimed to investigate whether any relationship exists between HEI scores and the risk of UC.

METHODS AND MATERIALS

Subjects

The protocol for this case-control study has been described previously[30]. Cases with recently diagnosed (<6 months) UC, as well as healthy controls aged 20-80 years were invited to participate by physicians at a clinic in Tabriz, Iran. In order to confirm a diagnosis of UC, patient medical records were reviewed prior to enrollment. Cases were excluded if they had any history of other gastrointestinal illnesses or carcinoma, autoimmune diseases, or any ongoing inflammatory disorders and infections.

Control subjects were selected from the orthopedic outpatient department at the same hospital. Controls and case groups were matched accordingly to gender and age (using 10-year groups). Exclusion criteria for the control group included ongoing gastrointestinal illnesses or symptoms (such as irritable bowel syndrome, gastroesophageal reflux, diarrhea, or abdominal pain), or noncommunicable conditions which may perceivably be linked to dietary intake (such as diabetes, cardiovascular disease, gout, or hyperlipidemia).

A trained interviewer conducted a face-to-face interview with each participant individually. Questionnaires to ascertain information about demography, past medical history, medications, dietary intake, alcohol consumption, smoking history, *Helicobacter pylori* status, and education were completed by participants. Education levels were classified as primary, secondary and high school, and those attending university. Participant weight was assessed in standing, shoeless subjects and was approximated to the nearest kilogram. Height was assessed by a non-stretch tape meter while participant was again in a standing, shoeless position fixed to a wall and it was approximated to the nearest centimeter.

Informed consent was obtained from each prospective participant by a physician prior to enrolment. The study was approved by the institutional ethics committee at the National Nutrition and Food Technology Research Institute of Shahid Beheshti University of Medical Science, Iran (1393/523).

Assessment of diet

Information on the typical diet of each subject was collected using a semi-quantitative food frequency questionnaire (FFQ) containing 168 food items that has previously been demonstrated to be valid and reproducible in an Iranian adult population [31]. In this FFQ, consumption frequency of food items was obtained on a daily, weekly, or monthly basis, and all data were transformed into the average monthly intake. Common portion sizes and household measures were used as portion sizes for each food item in the FFQ. participants whose total daily energy intake was outside of the credible range (men <800 or >4,200 kcal/day, women <600 or >3,500 kcal/day) were excluded[32, 33].

The Healthy Eating Index revised in 2015 (HEI-2015) includes 13 components including 1- Total Fruits, 2- Whole Fruits, 3- Total Vegetables, 4- Greens and Beans, 5- Total Protein Foods, 6- Seafood and Plant Proteins, 7- Whole Grains, 8- Dairy, 9- Fatty Acids, 10- Refined Grains, 11- Sodium, 12- Added Sugars, and 13- Saturated Fats [34]. Six items (1- Total Fruits, 2- Whole Fruits, 3- Total Vegetables, 4- Greens and Beans, 5- Total Protein Foods and 6- Seafood and Plant Proteins) each have five points and other items have ten points. Consequently, the HEI-2015 score ranges from 0 to 100.

To calculate HEI-2015 scores, food consumption values were obtained from the FFQ and different food groups translated to cup and ounce equivalents. The total fruits component included servings of whole fruits and fruit juice. Total protein foods component included servings of meat, poultry, eggs, seafoods, nuts, seeds, legumes (beans & peas) and soy products. Seafoods and plant proteins contained servings of seafoods, nuts, seeds, legumes (beans & peas) and soy products. Whole grains foods component included servings of legumes (beans & peas) and dark-green vegetables and total vegetables contained servings of legumes (beans & peas), dark-green vegetables, and all other vegetables. Fatty acids were included as a ratio of polyunsaturated and monounsaturated fatty acids to saturated fatty acids. Added sugars and saturated fats were converted to percent of total energy intake and other food components except for fatty acids were converted to represent the dietary intake of foods and nutrients by density as amounts per 1,000 kcal of intake.

Statistical analyses

Demographics and nutrient intake distribution were evaluated in control and UC case groups using independent two-tailed T test and $\chi 2$ analysis. The overall HEI-2015 score was subsequently categorized into quartiles based on the distribution among control participants. Logistic regression analysis was undertaken followed by adjustment for potential confounding variables. Potential confounding's were determined by literature review. The included variables were age, gender, weight, consumption antibiotic, non-steroidal anti-inflammatory drugs (NSAID) consumption, smoking, education and history of *H. pylori* (groups were matched accordingly to gender and age). The lowest quartile of HEI-2015 was thereby taken to be the reference category and odds ratios (ORs) were estimated with 95% confidence intervals (95% CIs). The HEI-2015 quartiles were then assessed for an associative trend with UC OR. All statistical analyses were completed using SPSS (v23, IBM Corp.) with significance accepted at $\alpha=0.05$ for all analyses.

RESULTS

Subjects

Fifty-eight patients with recently diagnosed (<6 months) UC and 123 healthy controls (all Caucasian) were recruited (Table 1). The mean age and BMI for cases and controls were 36.17 ±13.66 and 36.20 ±11.89 years and 25.11 ±3.93 and 25.68 ±3.98 kg/m^2, respectively (p=0.32 and p=0.30). In UC group, 3.4% participants had history of appendectomy, 3.4% used Nonsteroidal anti-inflammatory drugs, and 5.2% consumption alcohol. These amounts were zero in control groups.

Overall dietary patterns in cases and controls

The average micro- and macronutrient intakes for each group were calculated (Table 2). Mean total calorie intake ± SD were 2825.75±586.39 kcal per day in cases and 2573.38± 554.31 kcal per day in controls (p=0.01). In addition, UC participants consumed higher daily quantities of total protein (p=0.02), total fat (p=0.01), saturated fatty acids (SFA) (p=0.02), mono unsaturated fatty acids (MUFA) (p=0.01) and poly unsaturated fatty acids (PUFA) (p=0.05). Mean healthy eating index in control group and UC group were 64 and 62, respectively (p=0.23). There are not any significant differences between total carbohydrate intake (p=0.08), cholesterol (p=0.28), vitamin D (p=0.20), vitamin C (p=0.13), and vitamin E (p=0.32).

HEI-2015 scores for cases and controls

Cases and controls were classified into quartile categories based on their HEI-2015 score. The bracketing for each category was as follows: Q1<62, Q2=62-66, Q3= 66-71, and Q4≥71. The odds ratio for UC estimates associated with each HEI-2015 quartile were derived (Table 3), with Q1 acting as the reference category (*i.e.* OR = 1).

The odds ratio for the highest quartile of the HEI-2015 score was not different to the lowest quartile in the crude model (OR = 0.46, 95%CI: 0.18–1.12). However, the highest quartile differed from the lowest quartile in a fully adjusted model (adjusted for age, gender, weight, antibiotic prescription, NSAID use, smoking, education, and *H. pylori*) (OR = 0.34, 95%CI: 0.12–0.96). Finally, the odds ratio for UC based on HEI-2015 was also found to be statistically significant in the fully adjusted model (p=0.04; Figure 1).

DISCUSSION

In the present study, the widely-validated HEI-2015 tool was applied to FFQ data acquired from a study of healthy controls and subjects recently diagnosed with UC in order to assess whether there existed a relationship between the degree of healthy eating and disease. The current data arising confirms many of the dietary associations previously linked with UC, demonstrating that those with UC had a substantially higher mean daily energy intake and consumed elevated levels of several micronutrients, protein and fat - including SFA, MUFA and PUFA. In addition, a significant inverse trend was elucidated between the healthy eating index category and odds ratio of UC, suggesting that unhealthy eating may be a cause or consequence of the disease.

There are several notable strengths of the present study. Firstly, the models applied in the current study took into account numerous potential confounders. In addition, the use of the two validated assessment tools, the FFQ and HEI-2015, provides credibility and reliability to the results arising. Moreover, as the HEI-2015 is an energy adjusted index the inverse association observed is more likely due to dietary composition and not driven solely by increased energy intake. To our knowledge, the current study represents the first use of the HEI-2015 tool to

assess and compare healthy eating habits amongst patients with UC and healthy controls, thereby providing future investigators with crucial information regarding potential targets of intervention for prevention, risk reduction or management of UC.

Diet is a potent modulator of health and disease, in particular in conditions affecting the gastrointestinal tract. Numerous studies have identified putative links between specific dietary patterns and development of inflammatory conditions, including UC [35-37]. In this case-control study, a distinct disparity in energy intake was identified between healthy controls and UC participants. Although healthy controls averaged 2,573 kcal/d, the UC group displayed a mean intake of 2,825 kcal/d, which is substantially higher than the recommended daily intake of an adult male (*i.e.*, 2,500 kcal/d). Superficially, the result appears to be in direct opposition with a previous cross-sectional study investigating the eating habits of patients with UC, in which participants were found to ingest fewer calories than the recommended daily intake [38]. However, these cohorts differ crucially in their duration of disease (*i.e.*, 0-20+ years in the aforementioned study and <6 months in the present study), suggesting that dietary habits may evolve over time with disease course. The clear increase in energy intake observed in UC participants leads us to postulate whether increased energy intake may predispose to or precipitate UC development in this population.

Alternatively, since the mean BMI was similar across cases and controls, we may consider whether the intestinal inflammation incurred in UC may lead to malabsorption, thereby necessitating consumption of a greater amount of energy for maintenance requirements. However, the small intestinal malabsorption which frequently accompanies UC is thought to be driven by neuro-immune pathways that are likely to arise only in the chronic, rather than acute (*i.e.*, <6 months), disease state [39]. Furthermore, the results of the aforementioned observational UC study demonstrated that patients experience significant food aversion in chronic UC [38], indicating that this hypothesis is not likely substantiated.

In addition to an absolute increased in energy intake, protein and fat macronutrients were elevated in the diet of patients with UC compared to the healthy controls. Indeed, protein intake has repeatedly been linked to an increased risk of UC in a diverse range of cohorts [40]. A previous questionnaire-based study of 67,58middle-aged French women noted that risk of IBD was significantly and positively associated with protein intake, in particular proteins derived from

meat [41]. The investigators postulated that the breakdown of such dietary proteins into toxic compounds by the resident colonic microbiota may be implicit in the initial pathogenesis of the disease . In line with this, a multitude of observational and interventional clinical trials have demonstrated the involvement of the colonic microbiota in both progression and remission of UC [42, 43].

Dietary fats have also been repeatedly proven to be important in UC risk assessment. In a similarly designed case-control study of UC, ingestion of increased levels of MUFA were found to be highly associated with disease development, at an odds ratio of 34 [44]. Conversely, the literature is somewhat fragmented in interpreting the role of PUFA in IBD pathogenesis, with studies demonstrating either protective [45] or predisposing effects [46]. However, this appears to be due primarily to the starkly differential effects of PUFA subgroups, as n-3 and n-6 PUFA, which seem to reduce and increase risk, respectively [47-50]. This effect is likely to be mediated primarily by the effects of such fatty acids on inflammation, as the inflammatory potential of diet has been shown previously to impact substantially on the rate of UC [51]. The ratio of n-3: n-6 was not readily discernable from the current dataset and, therefore, the relationship is not explored further in the current population.

erhaps most intriguing of the result uncovered by this data is the inverse association observed between the energy-adjusted HEI-2015 score quartiles and odds ratio of UC in the adjusted model. While previous studies have focused on specific micro- and macronutrients in search of culpable dietary components, little data is available considering in more global terms, such as the healthy eating index. Indeed, this leads us to question whether less healthy dietary behavior is the cause or a consequence of UC. Although this question cannot be directly addressed within the design of the present study, as the participants were in the early stages of the disease, it may be speculated that these dietary disparities may have existed prior to the onset of UC, rather than being a result of disease.

It must be noted that this study has several inherent limitations. Firstly, although the HEI-2015 is a well-validated and evolving tool for the evaluation of dietary quality [52], it takes its foundations from the Dietary Guidelines for Americans and, therefore, may not be as reliably

applied to non-American populations. Secondly, due to the nature of FFQ, such studies may suffer from a degree of participant recall bias. However, the protocol was designed to limit the impact of such factors. Finally, as with all observational cross-sectional studies, causation cannot be attributed to the phenomena observed, but may direct future efforts in the field. In particular, the effect of high healthy eating index dietary interventions on UC development rates could be assessed within a cohort of genetically predisposed individuals in a randomized controlled trial design.

CONCLUSION

This study demonstrates a clear association between less healthy dietary intake and UC risk. Specifically, UC patients displayed higher levels of daily energy, protein and fat intake, including SFA, MUFA and PUFA. These dietary intake patterns likely have direct and indirect impacts upon gastrointestinal health and, therefore, represent a targetable aspect of UC etiology, which should be addressed in future prospective clinical trials.

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FIGURES & TABLES

Fig 1: Trend of odds ratios for the association between HEI-2015 and ulcerative colitis.

Table 1. Sociodemographic characteristics of participants in a case–control study of Ulcerative Colitis [a]			
Characteristic	**Controls (n = 123)**	**Cases (n = 58)**	**P Value [b]**
Age	36.20 ± 11.89	38.17 ±13.66	0.32
BMI[c]	25.68± 3.98	25.11± 3.93	0.30
Gender			
Female	70 (56.9)	32 (55.2)	0.82
Male	53 (43.1)	26 (44.8)	
Highest Educational status			
Primary	6 (4.9)	7 (12.1)	
Secondary / High School	68 (55.3)	26 (44.8)	0.15
Tertiary / University	49 (39.8)	25 (43.1)	
History of Helicobacter pylori	7 (12.1)	1 (0.8)	0.01
Smoking	10 (8.1)	5 (8.6)	0.91
Appendectomy	0 (0)	2 (3.4)	0.03
NSAIDS [d]	0 (0)	2 (3.4)	0.03
Alcohol	0 (0)	3 (5.2)	0.01

a) Data are presented as mean ± SD or n (%).
b) Independent samples t-test was used for continuous variables and Chi-square test was used for categorical variables.
c) Body Mass Index
d) Nonsteroidal anti-inflammatory drugs

Table 2. Distribution of dietary intakes of macro- and micronutrients across cases and controls of Ulcerative Colitis study [a]			
Characteristic	**Controls (n = 123)**	**Cases (n = 58)**	**P Value [b]**
Total calories (kcal/day)	2573.38± 554.31	2825.75±586.39	0.01
Total protein intake (g/day)	87.80± 22.63	97.21± 29.82	0.02
Total carbohydrate intake (g/day)	350.75± 83.87	373.51± 76.55	0.08
Total fat intake (g/day)	96.31± 24.63	110.21± 32.14	0.01
Cholesterol (g/day)	267.40± 135.10	290.71± 140.85	0.28
SFA [c](g/day)	28.00± 9.59	31.56± 10.37	0.02
MUFA [d](g/day)	32.24± 8.00	38.15±12.17	0.01
PUFA [e](g/day)	22.93± 7.05	25.59± 9.17	0.05
Vitamin A (RAE/day)	676.47± 327.53	763.93± 609.30	0.28

Vitamin D (ug/day)	2.09± 1.53	1.79± 1.35	0.20
Vitamin E (mg/day)	17.48± 6.85	18.66± 8.63	0.32
Vitamin C (mg/day)	136.87± 64.34	121.68± 50.83	0.13
Vitamin B6 (mg/day)	1.90± 0.51	2.05± 0.54	0.06
Vitamin B9 (ug/day)	587.69± 154.74	599.20± 119.31	0.61
Vitamin B12 (ug/day)	4.76± 2.84	6.42± 6.47	0.06
Zinc (mg/day)	12.06± 3.36	14.08± 4.94	0.01
Copper (ug/day)	1.86± 0.54	2.09± 0.71	0.01
Magnesium (mg/day)	396.29± 101.93	427.67± 102.57	0.05

a) Data are presented as mean ± SD.
b) Independent samples t-test was used for continuous variables.
c) saturated fatty acids
d) Monounsaturated fatty acids
e) Polyunsaturated fatty acids

Table 3: Odds ratios and confidence intervals for the association between Heathy Eating Index 2015 and ulcerative colitis.					
Control / Case	27/19	32/13	30/15	34/11	
	Quarter1	Quarter2	Quarter3	Quarter4	P Value for Trend
Crude	Ref	0.57 (0.24-1.38)	0.71 (0.30-1.66)	0.46 (0.18-1.12)	0.13
Model 1[a]	Ref	0.61 (0.25-1.48)	0.68 (0.28-1.61)	0.42 (0.16-1.05)	0.08
Model 2[b]	Ref	0.66 (0.26-1.71)	0.61 (0.23-1.59)	0.34 (0.12-0.96)	0.04

a) Adjusted for age.
b) Adjusted for age, gender, weight, consumption antibiotic, NSAID consumption, smoking, education, *H. pylori* status and oral contraceptive drug (for women).2